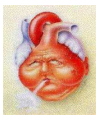
Cardiac hypertrophy and failure



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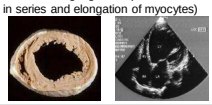
Left ventricular hypertrophy

1. **Ventricular remodeling**

- changes in *size, shape, structure* and *physiology* of the heart after myocardial injury
- compensatory mechanism for the increased preload and afterload
- a series of histopathological and structural changes occur in the left ventricular (LV) myocardium, which lead to a progressive decline in LV performance
- first step is the development of **ventricular hypertrophy** in an attempt to maintain systolic wall stress
- *pressure* overload (hypertension, aortic stenosis) - **concentric hypertrophy**
  (parallel replication of myofibrils and thickening of individual myocytes)

- *volume* overload (aortic or mitral regurgitation) - **ventricular dilatation**
  (replication of sarcomeres in series and elongation of myocytes)



Pathophysiology of LV remodeling

Remodeling stimuli
(wall stress, cytokines, neurohormones, oxidative stress)

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- myocyte growth and hypertrophy
- alterations in: - extracellular matrix
  - myocardial energetics
  - Ca-handling proteins (SERCA2, phospholamban)
- myocyte death (necrosis and apoptosis)
- fetal gene expression

⬇

Increase in myocardial mass (LV hypertrophy)
Chamber dilatation
Interstitial matrix accumulation (fibrosis)

⬇

SYSTOLIC *and/or* DIASTOLIC DYSFUNCTION

Heart failure - Definition

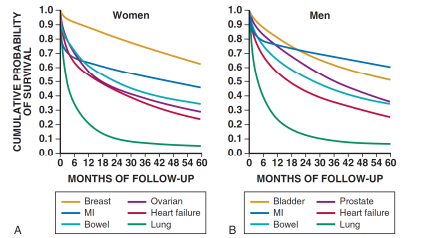
European Society of Cardiology/Heart Failure Association - 2016:

Heart failure is a **clinical syndrome** characterized by typical *symptoms* that may be accompanied by *signs* caused by a *structural and/or functional cardiac abnormality*, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

ESC Guidelines, *European Heart Journal* (2016) 37, 2129–2200.

Epidemiology and prognosis of heart failure

- 15 million patients with heart failure in Europe (5 million patients in the U.S.)
- prevalence 2% (6-10% above 65 years)
- accounts for 5% of the acute hospitalizations (1 million patients/year in the U.S.)
- 2% of the total health expideture (5,4% in the U.S., 38 billion USD/year)
- incidence doubles in every 10 years
- high mortality (20-80%), (300.000 patients/year in the U.S.)



Five-year survival following a first admission for heart failure, myocardial infarction, and the four most common sites of cancer specific to men and women.

Modified from Stewart S, *Eur J Heart Fail* 3:315, 2001.

Aetiologies of heart failure I.

1.

DISEASED MYOCARDIUM		
Ischaemic heart disease	Myocardial scar	
	Myocardial stunning/hibernation	
	Epicardial coronary artery disease	
	Abnormal coronary microcirculation	
	Endothelial dysfunction	
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-inflammatory drugs, anaesthetics.
	Radiation	
Immune-mediated and inflammatory damage	Related to infection	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).
	Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss).
Infiltration	Related to malignancy	Direct infiltrations and metastases
	Not related to malignancy	Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease).
Metabolic derangements	Hormonal	Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.
	Nutritional	Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity.
Genetic abnormalities	Diverse forms	HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies.

ESC Guidelines, *European Heart Journal* (2016) 37, 2129–2200.

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EMF = endomyocardial fibrosis; GH = growth hormone; HCM = hypertrophic cardiomyopathy; HES = hypereosinophilic syndrome; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; LV = left ventricular.

Aetiologies of heart failure II.

2.	**ABNORMAL LOADING CONDITIONS**		
	Hypertension		
	Valve and myocardium structural defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve diseases.
		Congenital	Atrial and ventricular septum defects and others (for details see a respective expert document).
	Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis Pericardial effusion
		Endomyocardial	HES, EMF, endocardial fibroelastosis.
	High output states		Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.
	Volume overload		Renal failure, iatrogenic fluid overload.
3.	**ARRHYTHMIAS**		
	Tachyarrhythmias		Atrial, ventricular arrhythmias.
	Bradyarrhythmias		Sinus node dysfunctions, conduction disorders.

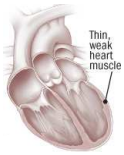
ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EMF = endomyocardial fibrosis; GH = growth hormone; HCM = hypertrophic cardiomyopathy; HES = hypereosinophilic syndrome; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; LV = left ventricular.

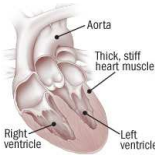
ESC Guidelines, *European Heart Journal* (2016) 37, 2129–2200.

Clinical forms of heart failure

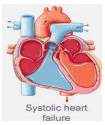
- Right vs. left heart failure (backward vs. forward failure)
- Low-output vs. high-output heart failure
- Acute vs. chronic heart failure
- Heart failure with reduced (**HFrEF**), mid-range (**HFmrEF**) and preserved (**HFpEF**) ejection fraction (EF) (2016-)

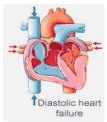
HFrEF (EF<40%)	HFmrEF (EF 40-49%)	HFpEF (EF>50%)

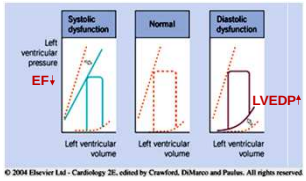


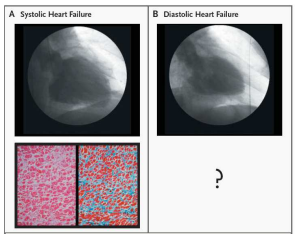


HFrEF vs. HFpEF: distinct heart failure phenotypes



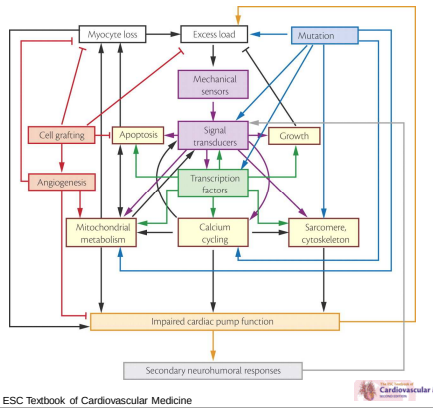






Redfield MM. *NEJM*, 2004; 350, 1930-1931.

Biological circuits in HFrEF



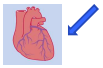
McMurray, J. et al. ESC Textbook of Cardiovascular Medicine

Activation of the Frank-Starling mechanism and the neurohumoral system in HFrEF

1. The **Frank-Starling** mechanism (the law of heterometric autoregulation)
   - rise in preload increases the force of contraction, thereby helping restore stroke volume
2. Activation of **neurohumoral systems**

   The extent of activation of the autonomic nervous system and endogenous hormone production seems to vary with the clinical state of the patient.

   a/ Circulatory reflexes (increased vasoconstrictor activity)
   b/ **Sympathetic nervous system activation**



Myocardial effects

- Downregulation of β_1-receptors
- Increased ic. Ca^{2+} concentration
- Arrhythmias
- Cardiomyocyte apoptosis
- Interstitial fibrosis

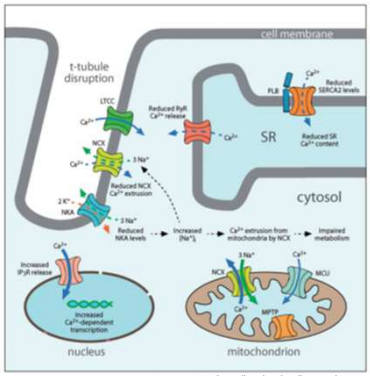
Renal effects

- RAAS activation
- Renal vasoconstriction
- Impaired natriuretic answer

Vascular effects

- Increased peripheral vasoconstriction

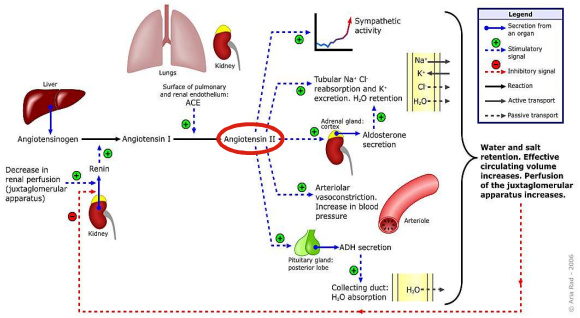
Altered Ca^{2+}-signaling and contractile deficit in failing cardiomyocytes



Aronsen JM. *Scandinavian Cardiovascular Journal*, 2016: 50:2, 65-77.

Activation of RAAS in HFrEF

c/ **Activation of the Renin-angiotensin-aldosterone system (RAAS)**



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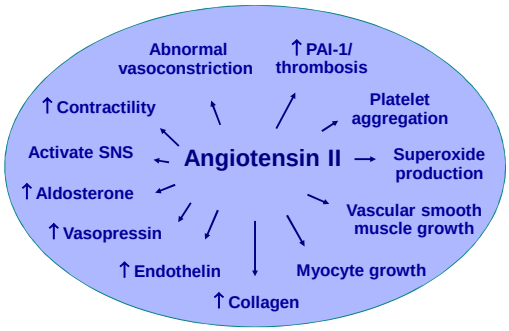
Pathophysiologic effects of angiotensin II

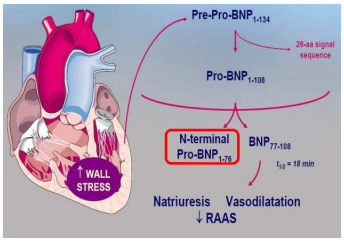


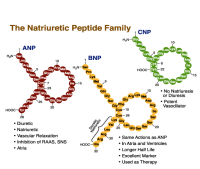
Modified after Burnier & Brunner, *Lancet*, 2000

The role of natriuretic peptides in heart failure

d/ **Natriuretic peptides**

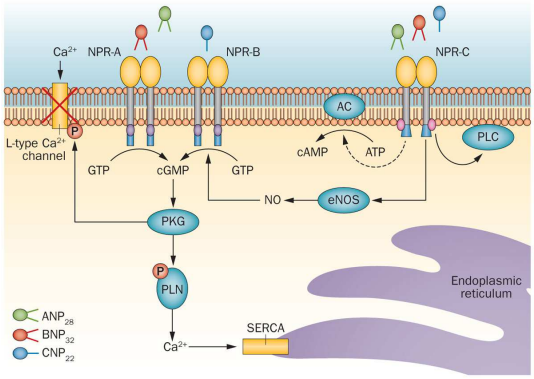
- ANP, BNP, NT-proBNP, CNP, dendroaspis, urodilatin
- released from cardiomyocytes in response to atrial and ventricular wall stretch





Other hormones: vasopressin, prostaglandins, bradykinin, histamine, EDRF, endothelin-1, relaxin, adrenomedullin, urocortin, apelin, etc.

Natriuretic peptides: signal transduction pathways



Zois NE., *Nature Reviews Cardiology* 11, 403–412. (2014)

Natriuretic peptides: complex physiological effects

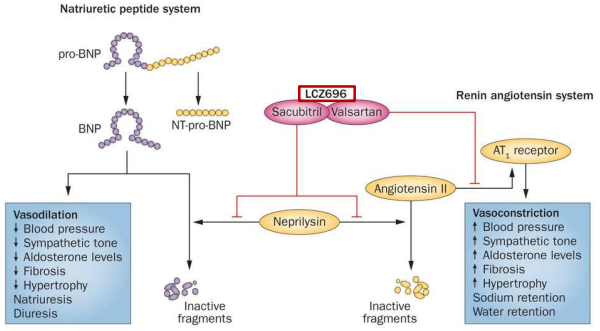
- Inhibition of the sympathetic nervous system and the RAAS
- Natriuretic and diuretic effects (kidney and distal tubules)
- Vasodilatory effects, smooth muscle relaxation (decreased PVR)
- Vascular system: antiproliferative, antifibrotic and antihypertrophic effects
- Myocardial effects: direct lusitropy (relaxation)

Heart failure: clinical importance of natriuretic peptides

1. Diagnosis
2. Prognosis
3. Follow-up the effectiveness of HFrEF therapy
4. Therapy (recombinant human BNP (nesiritide), ARNI)

Natriuretic peptides, as therapeutical targets: ARNI

LCZ696 is an **ARNI** (Angiotensin Receptor Neprilysin Inhibitor) which reduces the strain on the failing heart, enhances the levels of natriuretic and other endogenous vasoactive peptides, while also inhibits the RAAS.

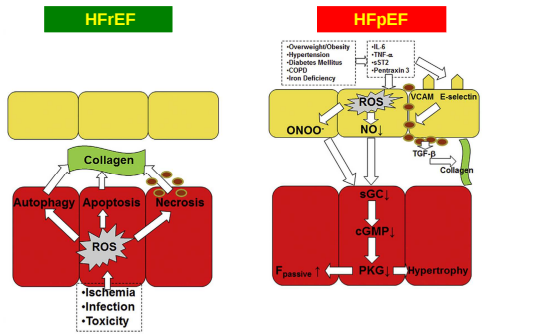


Pathophysiology of heart failure: Maladaptive responses

„Overshoots" of compensatory responses in HF:

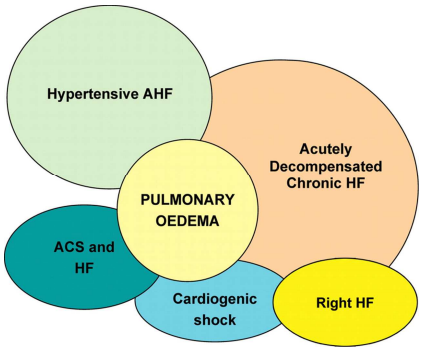
1. Vasoconstriction → decrease in cardiac output
2. Increase in heart rate → increase in energy consumption
3. Hormonal (renal) responses → excessive fluid accumulation
4. Hypertrophy → impaired energetics, ischaemia
5. Increase in collagen content → impaired relaxation

HFrEF vs. HFpEF: distinct pathophysiology - the novel paradigm



Paulus WJ, JACC, 2013, 62, 263-271.

Common clinical manifestations of heart failure



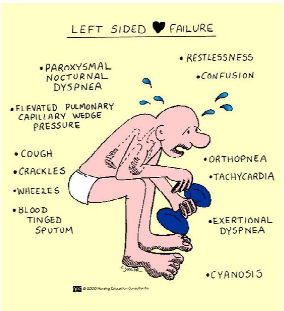
Dickstein K. et al., *Eur Heart J* (2008) 29 (19): 2388-2442.

Symptoms – Left sided failure

Backward failure:

- **Dyspnea**
  - On exertion and/or at rest
  - Paroxysmal nocturnal dyspnea (PND)
  - Orthopnea
  - Pulmonary edema
  - Cheyne-Stokes

- **Pulmonary crackles** (Killip classification)
- **Cough, sputum** („asthma cardiale")

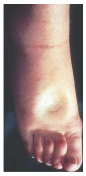


Forward failure:

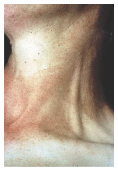
- **Hypotension**
- **Pallid and cold limbs** (vasoconstriction)
- **„Clear" lungs**

Symptoms – Right sided failure

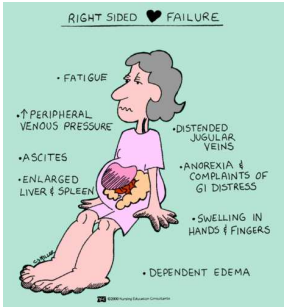
- Fatigue
- Peripheral edema, ascites
- Jugular vein distension
- Spleno- és hepatomegaly („cardiac cirrhosis")
- Gastrointestinal complains



Ankle swelling



Elevated jugular venous pressure



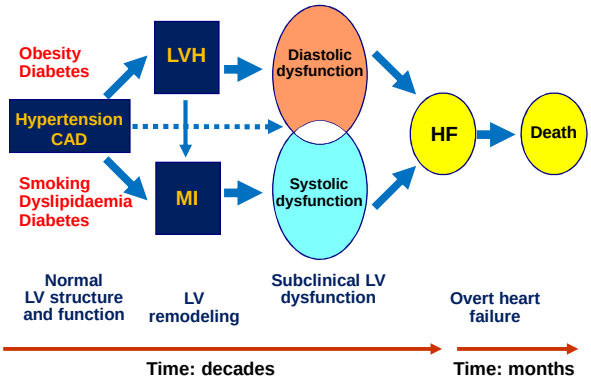
Classification of heart failure by symptoms relating to structural capacity (NYHA) or by structural abnormality (ACC/AHA)

NYHA functional classification	ACC/AHA stages of heart failure
Severity based on ***symptoms and physical activity***	Stage of heart failure based on ***structure and damage*** to heart muscle
Class I No limitation of physical activity. Ordinary physical activity doses not cause undue fatigue, palpitation, or dyspnoea.	**Stage A** At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.
Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.	**Stage B** Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.
Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.	**Stage C** Symptomatic heart failure associated with underlying structural heart disease
Class IV Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.	**Stage D** Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.

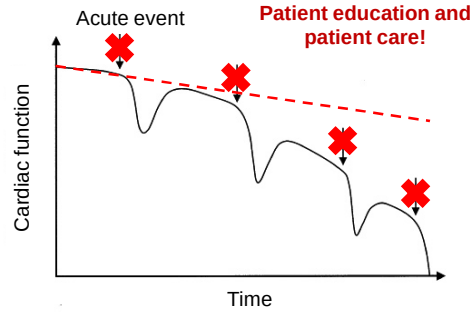
ACC, American College of cardiology; AHA, American Heart Association; NYHA, New York Heart Association.

(Dickstein K. et al., *Eur Heart J.* 2008; **29**: 2388–442.)

Progression of heart failure



Prevention of heart failure



Thank you for your attention!